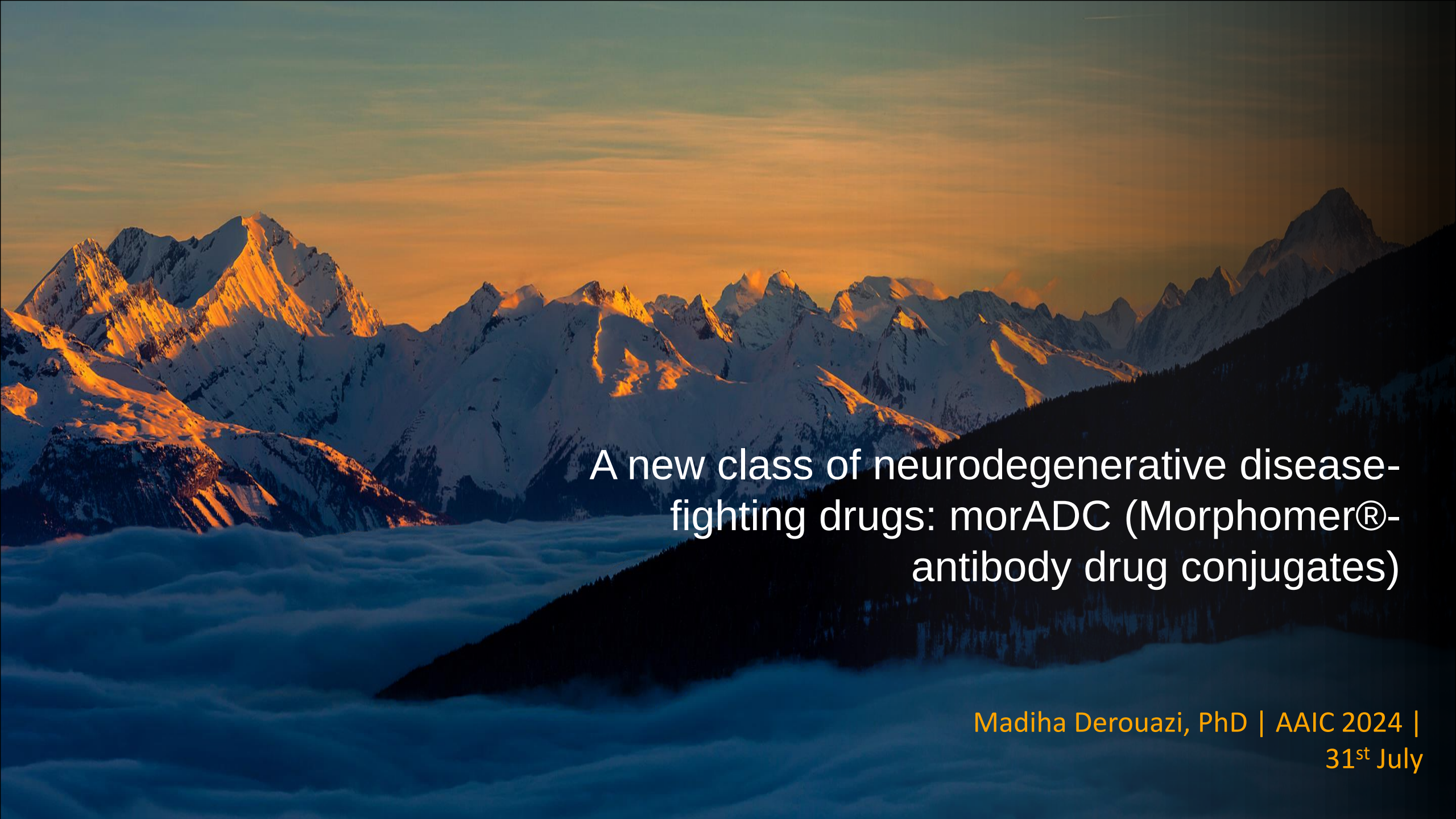

A new class of neurodegenerative disease-fighting drugs: morADC (Morphomer®-antibody drug conjugates)

Madiha Derouazi, PhD | AAIC 2024 |
31st July

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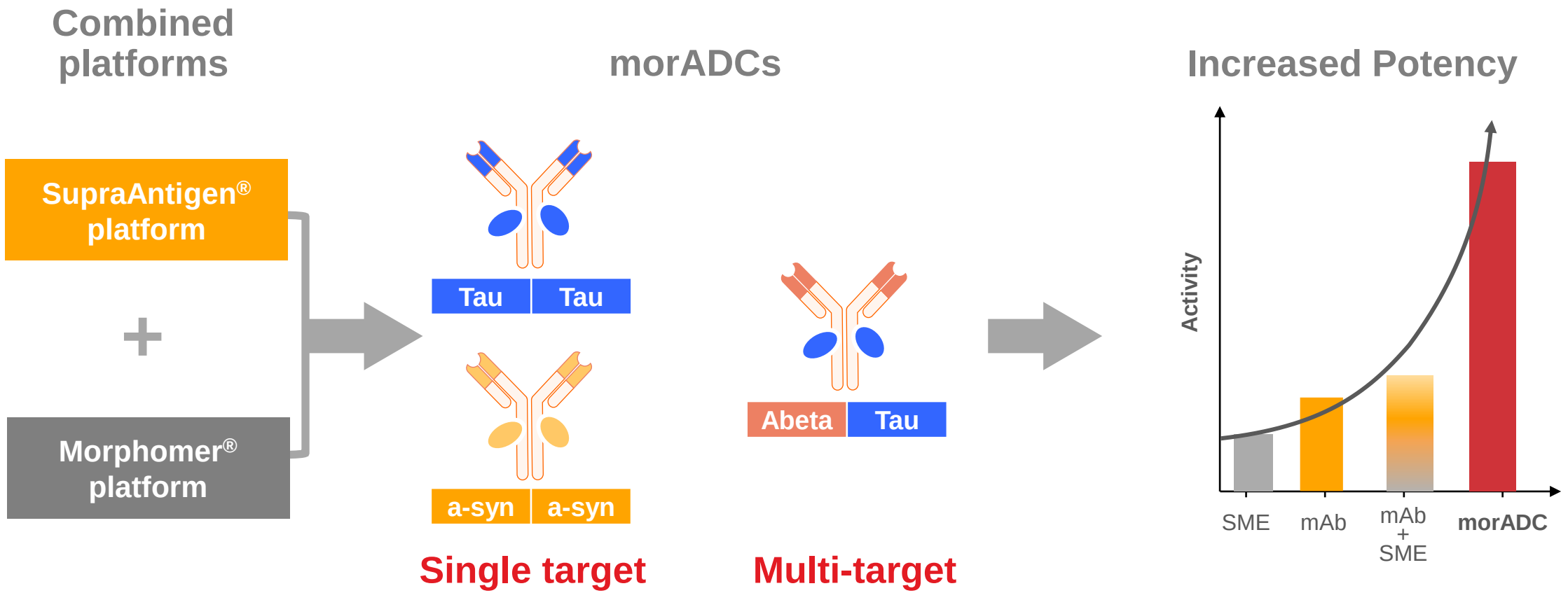
Conflict of interest disclosure

Madiha Derouazi is an employee of AC Immune SA entitled to stock options.

Morphomer® -antibody drug conjugates (morADC[1])

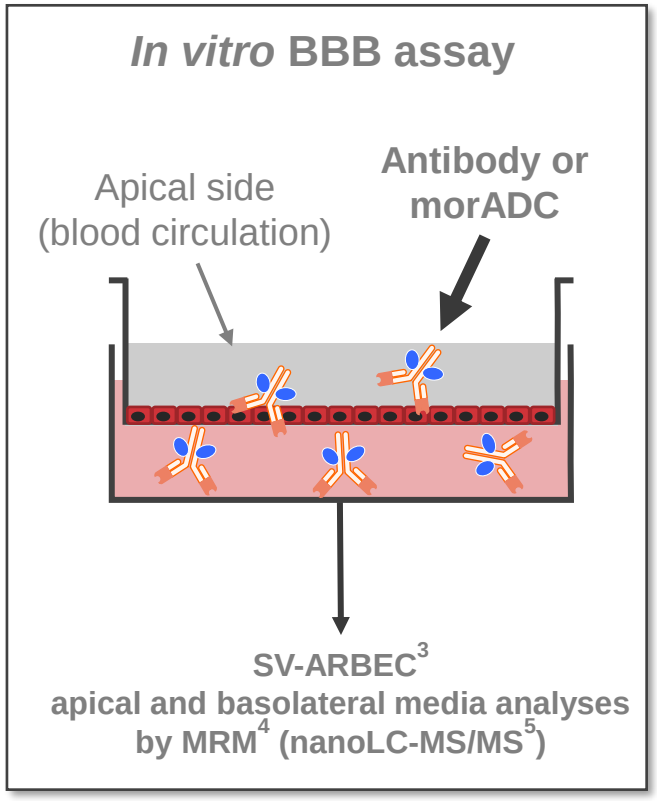
First-in-class molecules with highly synergistic effect

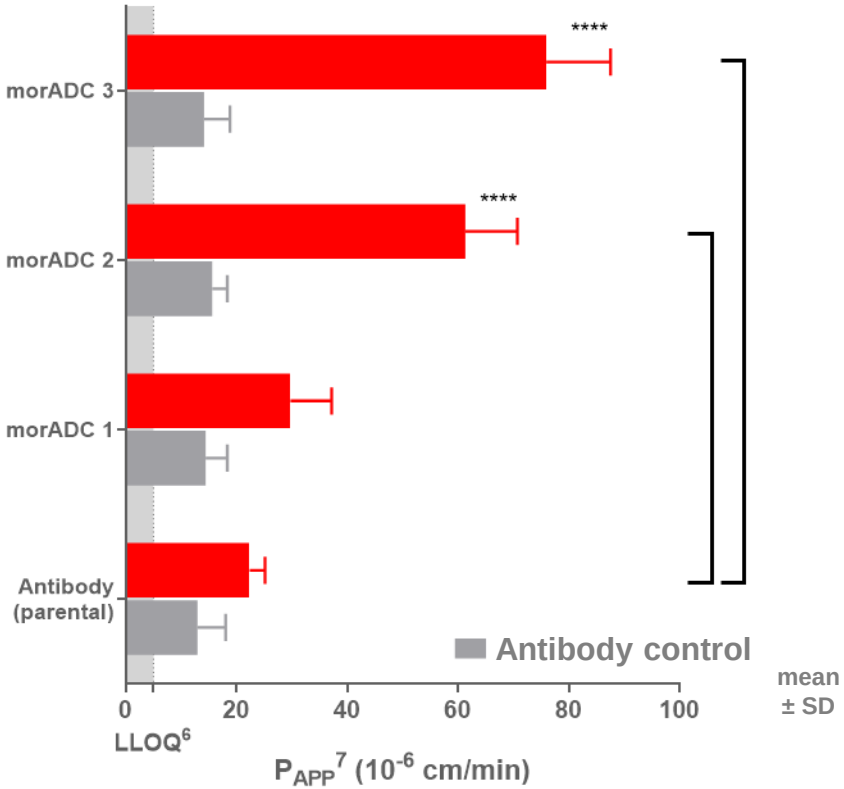


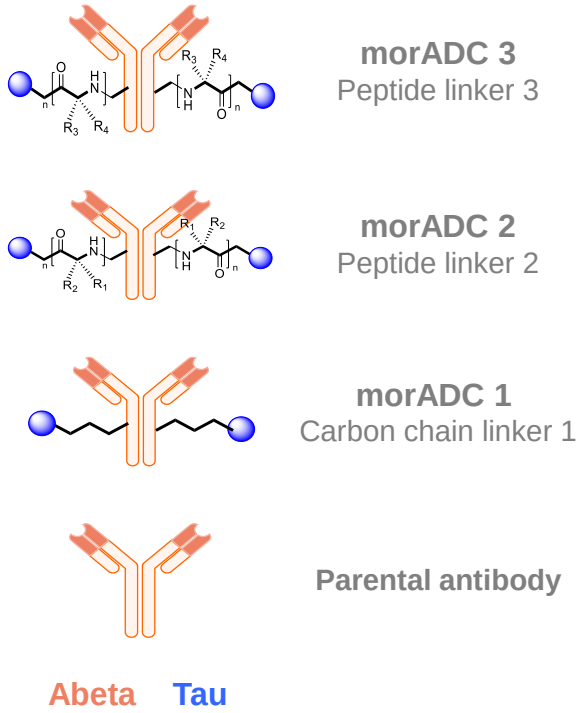
(1) Antibody drug conjugates; (2) Central nervous system

Impact of linker length/type on morADC[1] properties

Significant increase in an *in vitro* BBB[2] penetration assay







AC Immune unpublished data

- morADCs with peptide linkers displayed increased BBB permeability

(1) Morphomer-antibody drug conjugate; (2) Blood brain barrier; (3) Immortalized adult rat brain microvascular endothelial cells; (4) Multiple reaction monitoring; (5) liquid chromatography coupled tandem mass spectrometry; (6) lower limit of quantitation; (7) P_{APP}: apparent permeability

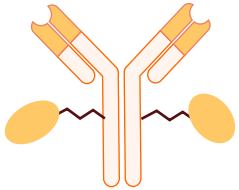
Brain penetrant Morphomer required for BBB[1] crossing morADCs[2]

Impact of Morphomer on brain penetration *in vitro*

ADC with brain penetrant Morphomer against a-syn

a-syn antibody

a-syn Morphomer

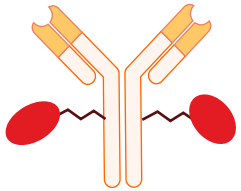


morADC 4

ADCs with brain non-penetrant Morphomers

a-syn antibody

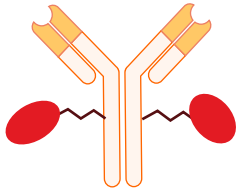
Morphomer 1



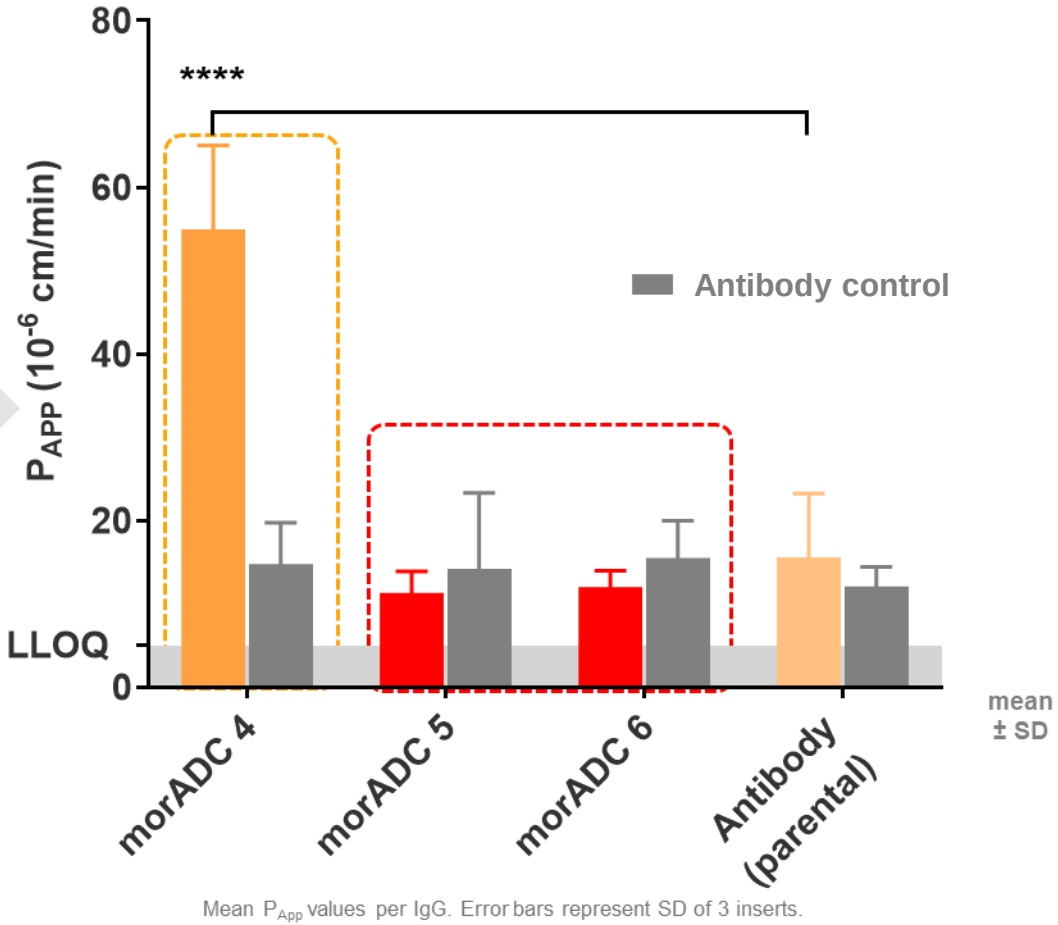
morADC 5

a-syn antibody

Morphomer 2



morADC 6



Mean P_{App} values per IgG. Error bars represent SD of 3 inserts.

AC Immune unpublished data

- Conjugation to a brain penetrant Morphomer is required for improved BBB penetration

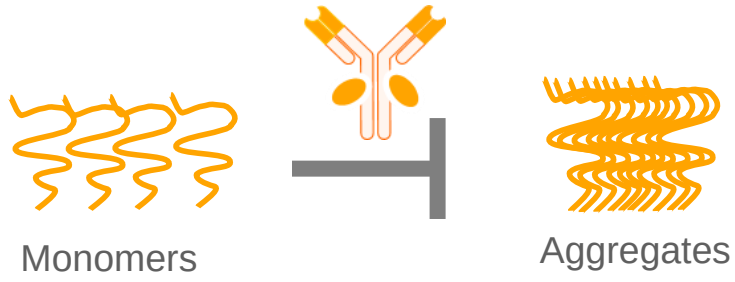
(1) Blood Brain Barrier; (2) Morphomer antibody drug conjugates

AC Immune

morADC synergy targeting alpha-synuclein

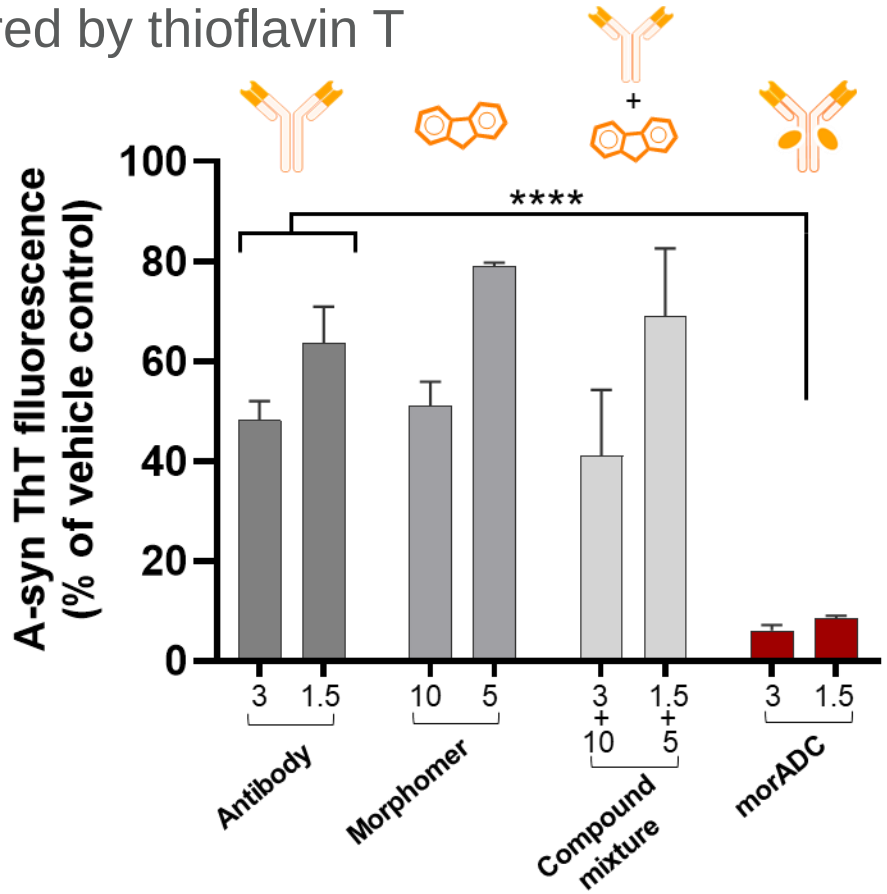
Inhibition of alpha-synuclein aggregation monitored by thioflavin T

Synergy targeting alpha-synuclein aggregates



IC_{50} values – ThT signal

Antibody	Morphomer	Mixture (1:3 ratio)	morADC
921 nM	9926 nM	2528 nM	121 nM



Mean ± SD
Two-way ANOVA
Tukey's test **** ≤0.0002

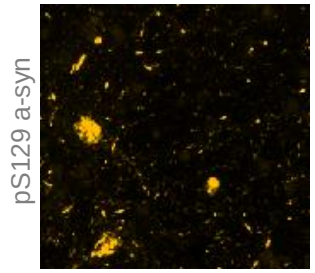
AC Immune unpublished data

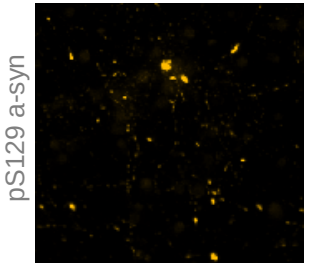
morADC is significantly more potent at inhibiting a-syn aggregation :

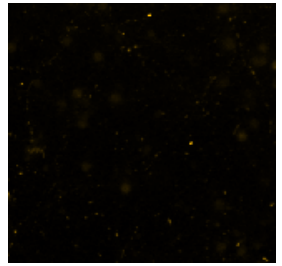
- **8-fold IC_{50} reduction compared to parental antibody alone**
- 80-fold IC_{50} reduction compared to Morphomer alone
- 21-fold IC_{50} reduction compared to the compound mixture

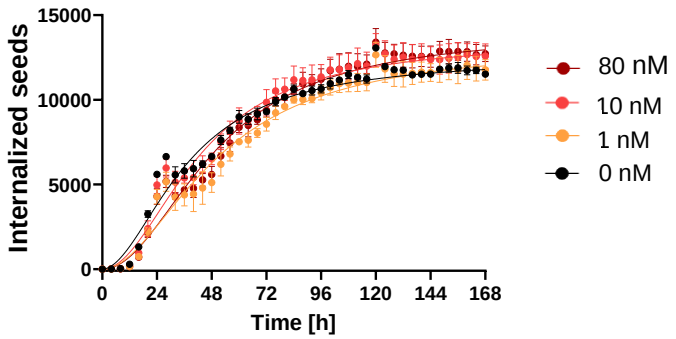
morADC inhibits seed uptake and a-syn aggregation

Kinetics of seed internalization in neurons and aggregates formed at endpoint



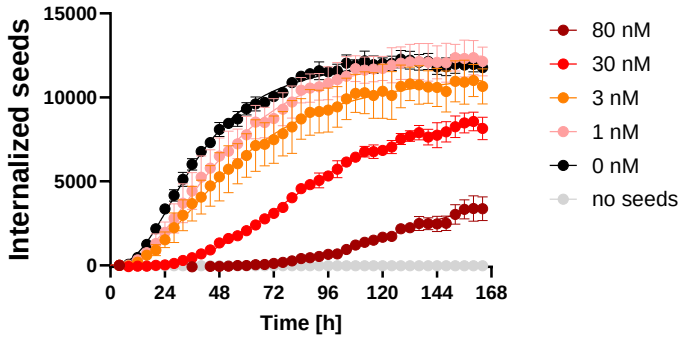






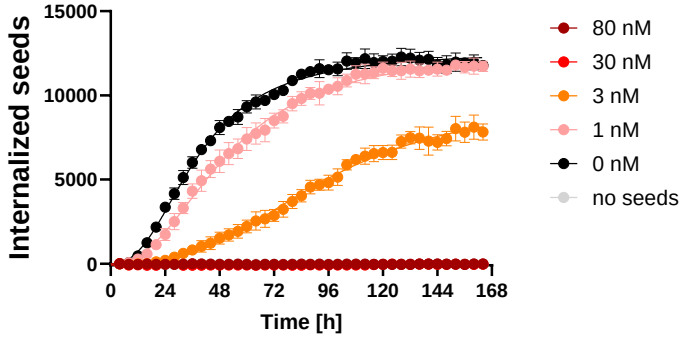
No effects

Control | Control



IC_{50} = 46.5 nM

a-syn



IC_{50} = 3.6 nM

a-syn | a-syn

- morADC has higher potency vs parent mAb with a 13-fold reduction of the IC_{50} for **seed uptake**
- Negative control[1] morADC has no effects on a-syn internalization

(1) Non-a-syn binding antibody conjugated to non-a-syn binding small molecule

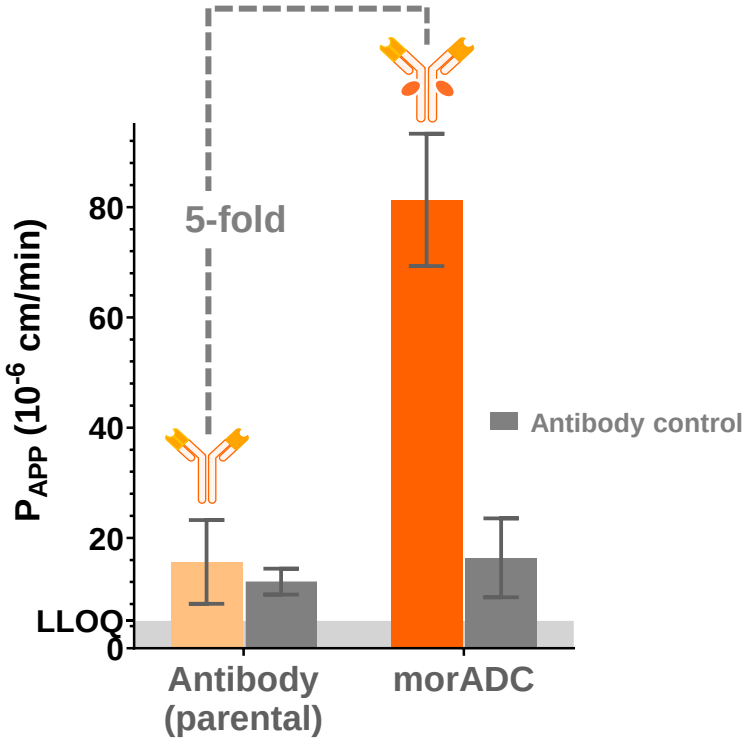
AC Immune unpublished data

AC Immune

In vivo CNS exposure study with a-syn/a-syn morADC

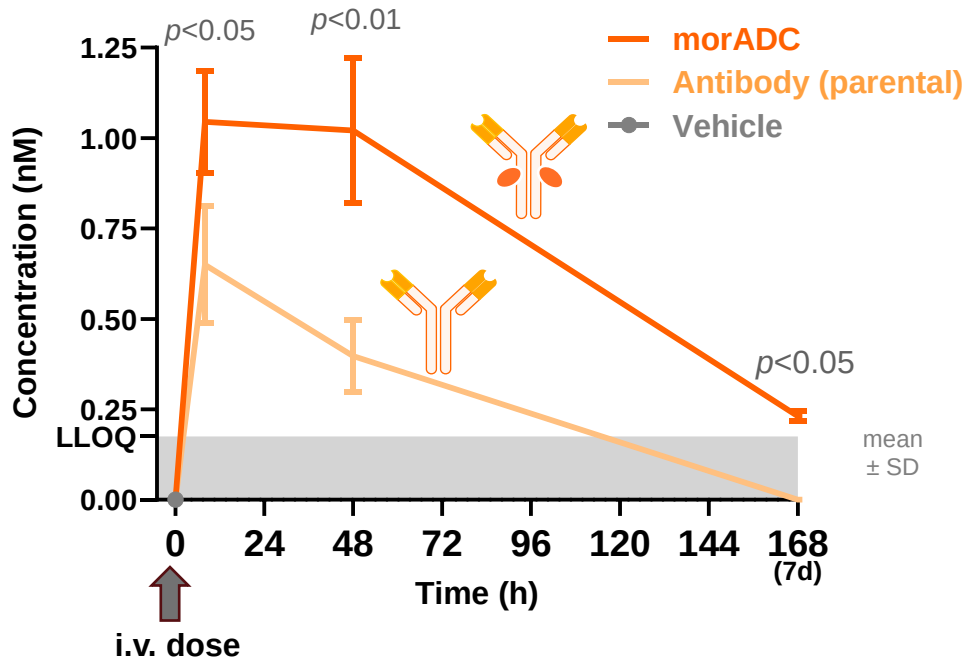
Comparison of antibody and morADC exposure in vessel-free brain parenchyma

In vitro BBB permeability



In vivo translation

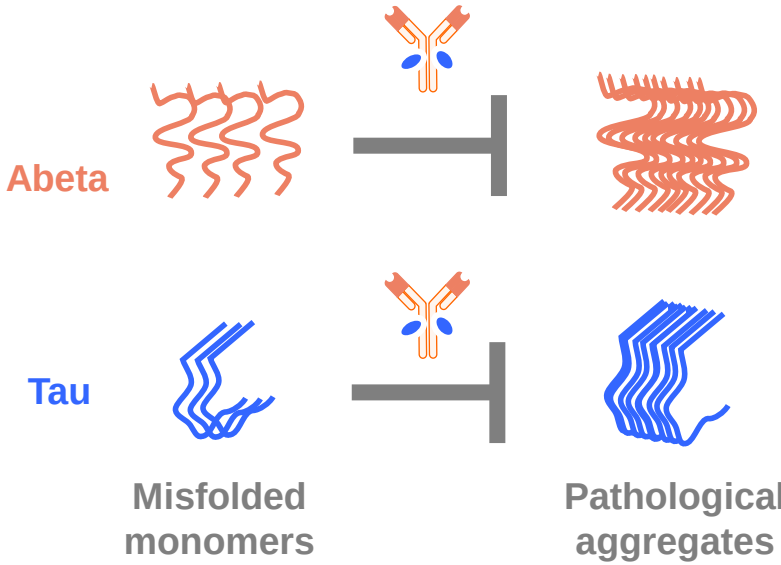
Vessel-free parenchyma exposure



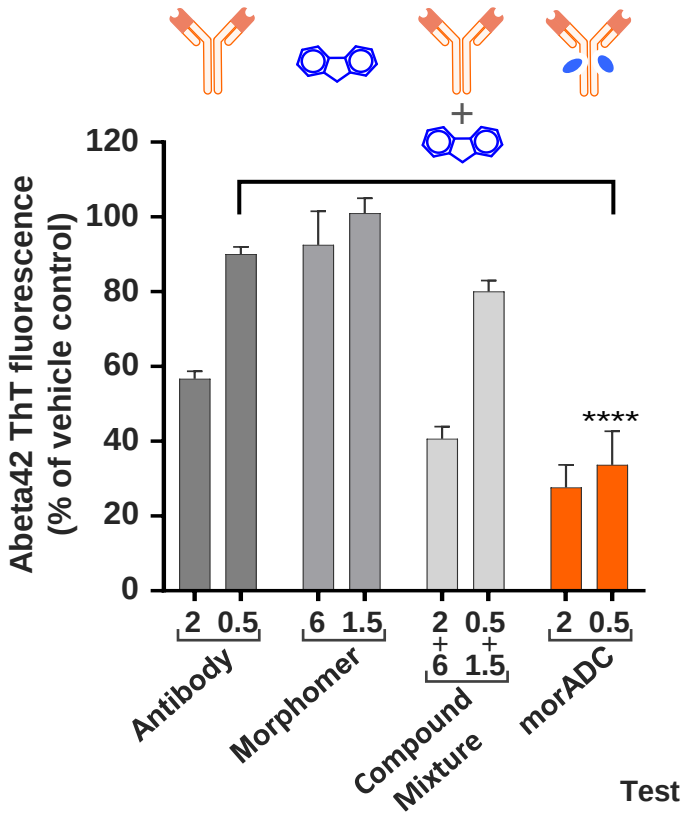
- Good translation from *in vitro* BBB permeability assay to *in vivo* brain exposure
- In addition, morADC increases CNS exposure compared to parental antibody

morADC[1] can target two different pathological proteins

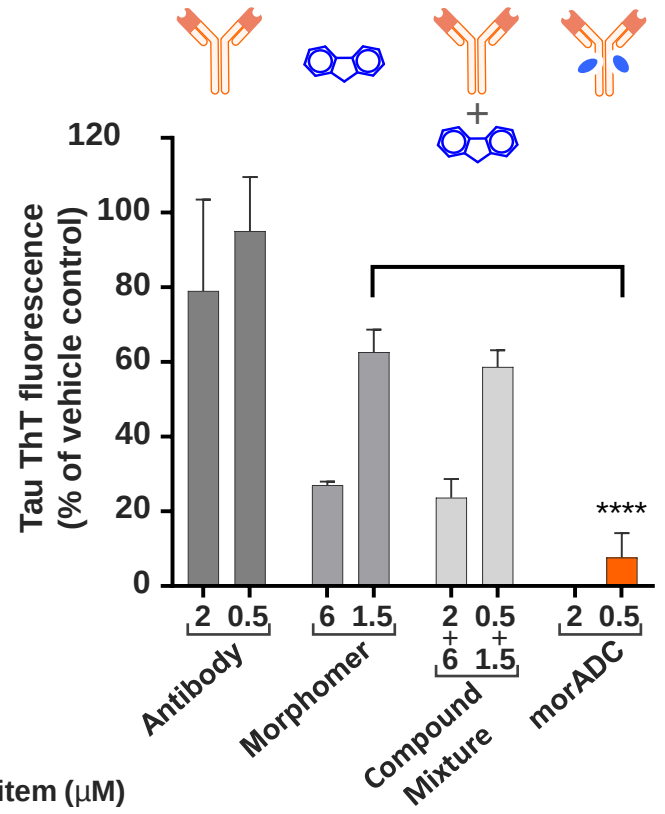
Inhibition of Abeta and Tau aggregation monitored by thioflavin T



Inhibition of Abeta42 aggregation



Inhibition of Tau aggregation



Test item (μM)

mean ± SD

AC Immune unpublished data

Dual and enhanced biological activity of the morADC:

- 3-fold higher inhibition of Abeta42 aggregation compared to parental antibody
- 15-fold higher inhibition of Tau aggregation compared to parental Morphomer

Conclusions

The morADC enable **single or dual-targeting strategies** (e.g. an anti-Abeta antibody combined with an anti-Tau small molecule) to deliver **combination therapy** in a single therapeutic agent

Single targeting morADC (a-syn/a-syn) shows anti-aggregation effects up to **80 times higher** than the parental molecules

Dual-targeting morADC (Abeta/Tau) shows **3 and 15 times higher** anti-aggregation effects for Abeta and Tau compared to the parental molecules, respectively

Additionally, **enhanced brain exposure in parenchyma (2 times higher)** was observed for the monoclonal antibody within the morADC

- The novel morADC concept results in important synergistic effects on the targeted proteinopathies

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